REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1-26 are pending. Claim 1 is amended herein. Basis for the amendment may be found throughout the specification and claims as-filed, especially in claim 2, as originally filed. No new matter is presented by way of the present Amendment.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-5 and 7-21 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The Office Action states that the claims are indefinite because claim 1 purportedly fails to define R_2-R_4, and that for examination purposes, R_2-R_4 are considered to be either hydrogen atoms or alkyl residues comprising from 1 to 5 carbon atoms. Applicants have amended claim 1 herein to recite the definitions of R_2-R_4 as recited in claim 2 as-filed (*i.e.*, that R_2-R_4 are hydrogen atoms or alkyl residues comprising from 1 to 5 carbon atoms).

Applicants submit this rejection is obviated.

Rejections under 35 U.S.C. § 103

Claims 1, 3-5, 7-17, and 19-21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Egilmez *et al.* (*Gene Therapy*, 3: 607-614 (1996)) in view of Vehmeyer *et al.* (*Cellular Immunology*, 137: 232-238 (1991)).

Egilmez *et al.* is cited for purportedly disclosing a composition comprising cationic-liposome nucleic acid complex wherein the nucleic acid comprises a plasmid vector which operably encodes IL-2. Egilmez *et al.* purportedly disclose that human IL-2 encoding

nucleic acid is complexed with DC-cholesterol liposomes which can be transferred to tumors in vivo resulting in suppression of the tumor growth. However, Egilmez *et al.* fail to disclose that the composition comprises a phospholipid which meets the structural limitations set forth in the claims, such as hexadecylphosphocholine (HePC). The Office Action states that Vehmeyer *et al.* teaches that hexadecylphosphocholine is an antitumor compound having immunostimulatory activity such that it enhances T-cell responses via IFN-gamma induction, but only when HePC is used in combination with IL-2.

The Office Action states that it would have been obvious to the skilled artisan to modify the composition taught by Egilmez *et al.*, and that the skilled artisan would have been motivated to combine the teachings of Egilmez *et al.* and Vehmeyer *et al.* because Vehmeyer *et al.* indicates that the combination of HePC and IL-2 induces IFN-g and enhances T-cell antitumor responses. Applicants respectfully traverse.

As set forth in M.P.E.P § 2142, in order to establish a prima facie case of obviousness, three criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations.

In the present case, 1) the references fail to recite the elements of the claimed invention as amended herein, there is insufficient motivation to modify the cited references in the manner proposed in the Official Action, and there is no reasonable expectation of success of achieving the claimed invention.

The primary reference, Egilmez *et al.*, disclose the transfer of the human interleukin 2 gene complexed with either lipofection or DC-cholesterol liposomes to tumor xenografts, via

direct intratumoral injection. These experiments were done on SCID mice, *i.e.*, mice which lack immunocompetent B and T cells (*see* Egilmez *et al.*, page 612, lines 27-28). In describing the results of the experiments, Egilmez *et al.* disclose that complete tumor regression mediated by the mouse natural killer cells was seen, in 50-80% of the mice treated with the plasmid IL2-cDNA.

Vehmeyer *et al.* disclose that HePC is an antitumoral agent which acts by destroying the cell membrane and by interfering with signal transduction mechanisms in proliferating cells (*see* Vehmeyer *et al.*, page 232, last line to page 233, line 2). Furthermore, Vehmeyer *et al.* disclose that HePC is a T cell activator when it is used, *in vitro*, in combination with IL2. In fact, contrary to what the Office Action states on page 6, Vehmeyer *et al.* do not disclose or even suggest that HePC and IL2 enhance T cell antitumor responses. There are no experiments using tumoral cells provided by Vehmeyer *et al.* The T cell activation is only assessed by measuring IFN gamma production. T cell activity is not measured against tumoral cells. Vehmeyer *et al.* do not link the T cell activation of HePC to antitumoral activity. Instead, Vehlmeyer *et al.* merely state that further studies regarding HePC activity are needed (*see* page 237, last paragraph).

Thus, the cited references fail to provide the skilled artisan with motivation to modify the references, motivation to combine the references and with any expectation of success. The primary reference, Egilmez *et al.*, discloses that the antitumor effect of the human interleukin 2 gene is linked to NK cells, that T cells activation is not involved in tumor regression, and that HePC, used in combination with IL2, is a T cell activator. Therefore, the cited references do not provide the skilled artisan with motivation use a T cell activator (such as HePC), in combination with the IL2 gene disclosed by Egilmez *et al.* As Egilmez *et al.* disclose that T cell activation is ineffective for tumor rejection induced by IL2 expression, the

cited references also fail to provide the skilled artisan with an expectation of success.

In light of the above remarks, Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

Claims 1, 11, and 16-18 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Egilmez *et al.* in view of Vehmeyer *et al.* as applied to claims 1, 11, and 16 above, and further in view of Bischoff (WO 98/08489). Neither Egilmez *et al.* nor Vehmeyer *et al.* disclose that the combination product complex has a charge ration in the range of 0.05-20 or that complex has a diameter of between 20 and 800nm. The Office Action states that it would have been obvious to the skilled artisan to modify the composition taught by Egilmez *et al.* so that the composition comprised HePC with a reasonable expectation of success. Applicants respectfully traverse.

As stated above with regard to Egilmez *et al.* and Vehmeyer, both of these cited references fail to provide the skilled artisan with motivation to modify the references, motivation to combine the references and with an expectation of success. Egilmez *et al.* disclose that the antitumor effect of the human interleukin 2 gene is linked to NK cells, that T cells activation is not involved in tumor regression, and that HePC used in combination with IL2 is a T cell activator. Egilmez *et al.* further disclose that T cell activation is ineffective for tumor rejection induced by IL2 expression. Vehmeyer *et al.* fail to remedy these deficiencies, and so the cited references fail to provide the skilled artisan with an expectation of success. The cited references also fail to provide the skilled artisan with motivation use a T cell activator (such as HePC), in combination with the IL2 gene.

Bischoff fails to remedy the deficiencies of Egilmez *et al.* and Vehmeyer. Bischoff is cited to purportedly provide disclosure regarding the mean diameter size of the complex.

However, Bischoff fails to provide the motivation to alter the cited references and expectation of success that the other cited references fail to provide. As a result, the three cited references, alone or in combination, do not render the claimed invention obvious.

In light of the above remarks, Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

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